Current controversies in prenatal diagnosis 3: Industry drives innovation in research and clinical application of genetic prenatal diagnosis and screening.

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Running Head: Who drives innovation: academia or industry?

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What is already known about this topic:

1. Innovation and technological development have commonalities across all disciplines in terms of process, evaluation, and incorporation into use.
2. Many technologies have evolved through traditional methods such as research grant funding, individual and multicenter trials, followed by eventual introduction into common practice. Others have been significantly sped up by industrial resources and drive.

What this study adds:

1. The development of basic new concepts and procedures will very like continue to reside the academic environment.
2. As the pace of technological development has rapidly accelerated and academic support for such work has significantly diminished, corporate involvement, sponsorship, and partnering have become much more common and, particularly for laboratory techniques, are necessary to achieve progress at a rapid pace.
3. There is a balance that needs to be respected between the benefits and constraints of such industrial involvement that will require compromise on both sides to achieve an optimal environment.

INTRODUCTION (MARK EVANS)

The process of innovation has its own set of norms that can be applied across many disciplines regardless of whether the subject is a surgical procedure, imaging equipment, laboratory testing, or a hundred others[1,2]. In the United States, for example, the Federal government has agencies such as the Office of Health Research, Statistics, and Technology under which are the National Center for Health Statistics, National Center for Human Services Research, and the National Center for Health Care Technology (NCHCT). In the 1980's I was a Special Advisor to the Director of the NCHCT (initially focusing on AFP screening) whose mission has morphed into the Agency for Health Care Research and

Quality and focuses on the evaluation of new technologies and how they should be incorporated into medical practice. These agencies were created to provide the foundation upon which to understand problems and provide baselines against which to study new approaches. International Societies such as Health Technology Assessment International have likewise provided a framework for understanding the similarities and differences among seemingly disparate disciplines[3]. For example, a university or hospital can have a department of obstetrics and gynecology, which might have divisions of general obstetrics, general gynecology, maternal fetal medicine, reproductive endocrinology, and gynecologic oncology. A cancer center could have divisions of pediatric oncology, hematology/oncology, gynecologic oncology, etc. The two approaches to gynecologic oncology in this example start from somewhat different basic perspectives of mission and vision, but are adaptable to the specific technology and purposes.

There are two distinct phases of technology innovation in medicine. First, there is a phase of "development" in which a small number of investigators – traditionally but not necessarily at academic medical centers – have an idea, establish the concept for its use, test, maybe patent, publish, present, and create a demand for the technology/service. Then, as the demand grows, and the originators can no longer handle the demand, there is a phase of "diffusion." The technology moves out from the primary center to many other providers and sites. As the volume grows rapidly as inexperienced providers get in the game, but complication rates skyrocket [1,2]. Eventually, the level of performance improves as the concept is absorbed into practice, and there is a learning curve for the new providers.

While the above is most obvious for surgical procedures, it also applies to laboratory ones. The more subjective the process, the more that the pitfalls of diffusion apply. Many of

the new genetic laboratory technologies begin as laboratory developed tests (LDTs) with jury-rigged systems modified from other methods before there is sufficient standardization to have "kits," with US Food and Drug Administration (FDA) or Conformité Européenne (CE) clearance, which can have much of their quality control built in before the laboratory ever attempts to use them.

The debate question was: Industry drives innovation in research and clinical application of genetic prenatal diagnosis and screening. Speaking for the proposition was Tom Musci M.D. a maternal fetal medicine physician of Ariosa Diagnostics, and against was Joris Robert Vermeesh Ph.D. a molecular cytogeneticist of the Catholic University of Leuven. The moderator was Mark I. Evans, M.D. an obstetrician/gynecologist and medical geneticist from the Fetal Medicine Foundation of American and Mt. Sinai School of Medicine.

FOR (MARK EVANS*)

(Footnote: Written by Dr. Evans using Dr. Musci's speech and slides with his permission as basis).

Historically, students were always taught that one develops a rigorously based research hypothesis and then does experiments to prove or disprove the specific question. "Fishing expeditions" of just throwing stuff up against the wall and seeing what happens were disparaged as poor science. A disproportionate amount of advancements in medicine now come from applying technological advances from engineering, chemistry, optics, and other disciplines at a distance from genetics and other specialties of medicine. In such environments, applying a technology to multiple scenarios that are seemingly unrelated and seeing what it can do in any field is considered just as reasonable as pursuing physiologically

based hypotheses.[1,2] All academic grant funding is now very difficult to obtain, but for non-physiologic research technology tests, it is even more so. Since 1997, NICHD has seen the success rate of grant applications fall from 24.6% down to 11.5% (Table 1)[4]. It is even lower for investigator-initiated applications. Furthermore, NICHD overall funding and success of obtaining it are much lower than several other institutes such as General Medical Sciences, Heart, Lung, and blood, and neurologic disorders and stroke (Table 2)[5]. Adjusting for inflation has only made the support statistics even worse.

As a result of the above as well as general cut-backs in Medicare and Medicaid funding, the administrative dollars previously available to support academic research and investigators have dramatically shrunk. “Protected time” is now more myth than reality. Without access to new sources of research support, the academic triad of patient care, teaching, and research would be left with only the clinical practice leg because it pays the bills and balances the budget quarter by quarter. Long term strategic planning has largely disappeared.

There are numerous technologies that, were it not for considerable corporate funding the science, would not be available. One of the first genetic technologies largely developed by industry in the 1980’s and 90’s was fluorescent in situ hybridization for molecular identification of selected chromosome abnormalities [6]. There was initially considerable resistance among some circles to accepting at face value research from companies as compared to academic centers, but this got better over a period of some years as the data met all the same standards that would be expected from academic centers.

The most obvious industrial involvement in prenatal diagnosis has been the development of cell free fetal DNA (cffDNA) testing for non-invasive prenatal screening (NIPS) [7,8]. Over a decade two multicenter NICHD funded projects were not able to bring the analysis of fetal cells in maternal blood into clinical practice [9]. Following their completion, a number of companies entered into the field – often including investigators previously part of the NICHD consortium. When the science shifted from fetal cells to cell free fetal DNA and RNA, large amounts of applied research funding were obtained to capitalize and exploit new technology. No NIH funded mechanism could have worked with anywhere the speed and extent of the private sector enterprise. As a result, cffDNA has assumed a primary position in Down syndrome screening that would not have otherwise been possible [10].

The other major current technology that had enormous corporate involvement was array comparative genomic hybridization (aCGH) or chromosomal microarrays [11,12]. Much of the developmental work was done by industry including a number of significant publications. However, it was only through the NICHD collaborative study, that there was general acceptance of the much higher than originally expected incidence of abnormal fetal copy number variants (CNVs). This study was only possible, however, by the collaboration of the NIH with multiple companies performing microarrays who agreed to provide services, share data, and other ordinarily proprietary resources in order to make it work[11,12].

Similarly, pre-implantation diagnosis and screening would not have been possible without industry driven science [13]. In fact, in the United States, there was a federal funding moratorium for all IVF related research that forced the entire IVF enterprise to be created off- shore. This was because in the late 1970's and 80's there wasn't a reservoir of venture

capital that could be applied to research and development. Thus, without private support, such work would have been completely impossible.

Supporters of the academic model of "how it should be done" do not have a real answer for how they can survive without corporate and venture capital to support their research efforts. The Faustian bargain is that more and more industrial supported research and development is focused on application and product development rather than basic research to create new areas of opportunity.

AGAINST (JORIS VERMEESCH)

All key breakthroughs that have shaped prenatal and preimplantation genetic diagnosis over the last 50 years have been established in academia (Table 3). To exemplify the mechanism of this innovation process, I will focus on the two major revolutions that have taken place in prenatal genetic testing during the last 10 years, and for which I have had the privilege to be closely involved.

A first revolution was the development and implementation of arrays for prenatal genetic diagnosis. Array CGH, also termed molecular karyotyping or chromosomal microarrays, have largely replaced conventional karyotyping and this (r)evolution has occurred over the last 20 years. What were the innovations and who triggered them? At the end of the 1990's, FISH was well established. In the FISH procedure a single DNA fragment is fluorescently labeled and hybridized to chromosomes. Only copy number changes in that clone can be detected. Dan Pinkel and Peter Lichter reasoned that if FISH probes would be spotted on a glass slide and genomic DNA hybridized, a series of genomic loci could be interrogated for copy number changes [14]. It took subsequently another 5 years, before

academic scientists could optimize the method to work systematically and enable the detection of simple duplications and deletions. Under the guidance of Nigel Carter from the Sanger institute, a working group and a ring test was instigated and samples and procedures were exchanged [15]. Most importantly, the Sanger Institute shared the cloned human genome amongst all scientists. This methodology subsequently confirmed the hypothesis that a significant number of birth defects are caused by intrachromosomal copy number changes [16,17]. Subsequently, it was a small step from the use of chromosomal microarrays for the detection CNVs as the cause of constitutional developmental disorders to prenatal disorders. Following this proof of concept, translational academic researchers gathered to establish the first clinical studies, establish guidelines, and subsequently implement them into clinical care. In Belgium, the academic laboratories united to establish societally accepted approaches to deal with CNVs [18]. Knowledge of CNVs is in the public space, because scientific laboratories have shared this information publicly. Despite claims to the contrary, industry was not involved in making this transition from conventional karyotyping to chromosomal microarrays. Industry, starting 2006-2007, stepped in to mass produce arrays.

A second major revolution has been the development of noninvasive prenatal screening (NIPS) with cffDNA. Again, the original discovery that free floating plasma DNA contained placental fragments in pregnant women was made in an academic setting. Dennis Lo, first in Oxford and later in Hong Kong, played a key role in the initial discovery and implementation [7,8]. Subsequently, different prenatal screening strategies have been developed. All of them have been in the academic environment. The holy grail of NIPS was

the potential to discriminate fetal aneuploidies. Again, the main method was developed in an academic setting. The proof of concept that the fetal genome sequence can be reconstituted from the free floating DNA was made in academia. The key patents were mainly filed by academic laboratories.

The data fraud that temporarily derailed the enterprise was in the industry environment, fueled by a corporate rush to commercialize a product without any refereed publications and reasonable vetting[19]. It is highly likely that such would not have happened in an academic environment. There were multiple complaints at national and international meetings by highly respected "key opinion leaders" in and out of academia, that this was inappropriate. Such did not sway the company. However, it should be stated clearly that the fraud was actually discovered by internal, corporate academically trained professionals who with ethics and courage made it public and fixed it.

Rather than asking the question whether industry drives innovation, we have to ask the question why industry does not drive innovation? Leaders in research are artists who create visions and possibilities. Aberrant or unexpected results are not discarded but rather become the source for surprise, hypothesis building and subsequently, mainly through serendipity, new discoveries. Researchers see future potential in their innovation. At the first moment, however, techniques, methods, and insight do not yet exist beyond the researcher's mind. Subsequently, the method has to be proven to work. Grants are sought, which are only successful if there has already been some proof of concept. Hence, a researcher has to provide a proof of concept. Particularly for radically new concepts, often

even the leading colleagues do not recognize the potential, or do not believe the method can work.

Industry, in contrast, is by definition risk averse. Aberrant results are a nuisance and have to be avoided. To demonstrate this view, I turn to cffDNA performed by whole genome shotgun sequencing in commercial entities. In the first three years, those companies have reported to have performed over 1 million tests. Yet as of early 2015, only trisomies 13, 18,21 , and sex chromosome aneuploidies were clinically reported back routinely to patients. We performed 2000 tests and presymptomatically identified a non-Hodgkin lymphoma in a pregnant woman [20]. Since then, we have tested over 10,000 pregnant women and have identified 5 abnormal genome wide profiles consistent with the presence of different presymptomatic cancers [21]. Soon after these reports, maternal malignancies were detected in a joint commercial and academic driven project [22]. Extrapolated to the million patients performed in industry, 500 pregnant women with cancer did not obtain a diagnosis of cancer despite the data being present. In addition, we are reporting aneuploidies beyond trisomies 13, 18, and 21. It is becoming clear that those aneuploidies affect embryonic development and that reporting those may improve pregnancy management. Those observations were made in the academic laboratories, not in the industrial scale NIPS testing laboratories [21,23].

Industry actually has a propensity to hamper rather than to drive innovation! The majority of the patents were granted to university researchers and subsequently licensed to industry. Industrial players try to maximize their market share and block competition as much as possible. In addition, they try to extend the life span of their patents. In the NIPS world, we are all well aware of the dominant patent portfolio in some industrial hands. The

bigger companies can threaten the development of new methods and protocols by suing new players. Smaller laboratories or companies cannot pay the litigation costs and refrain from developments. If such a situation emerges, waiting until the patents expire or new breakthroughs which change the landscape is common.

Nevertheless, there is an important role for industry: First, a method/technique can be mass produced. This is not the role of academics nor of hospital laboratories; between 2002 and 2009 my laboratory printed over 10,000 BAC arrays. That was a huge effort, but clearly only sufficient to help 10,000 individuals and not the millions that are served today. Mass production of arrays has reduced the prices, improved quality, and increased the resolution. Second, academic methods/software/techniques usually provide proof-of-concept and are not meant to be brought into less academic environments. Industry can build the refinements required for specific end-users. Third, industry operates at a global scale and thus reaches a broader audience. The marketing machineries enable fast and global access to concepts that were developed locally. Finally, the large investment needed for large scale proof-of-concept, clinical validity, and utility studies which can be more easily obtained via industrial funding mechanisms (for an overview of large scale industry driven NIPT studies please refer to references [24,25]).

Cooperation between academics and industry is obviously needed. Both parties have to recognize each other's merits and limitations. In order to retain long term thrust in the health care machinery it seems to me important that academic independency is warranted. Academic researchers and medics have to be able to voice opposing views and act independent of industry. A too high dependence on industrial funding has the risk that this independence would be (perceived) not to exist.

CONCLUSIONS (MARK EVANS)

There is no doubt that each of the perspectives on whether industry drives innovation has a lot of data to support their respective positions. The reality is that both academia and industry want advancement in science – whether it be for knowledge sake, per se, better patient care and outcomes, academic development and promotion, or financial gain. There is no clearer example than the commercial rush to extend cffDNA to the low risk population with the abandonment of diagnostic procedures in a population for which the incidence of microarray detectable anomalies is actually 10 times that of Down syndrome.[10,26] The shift away from diagnostic procedures will actually cost more and find less as the increase in DS detection is much less than the potential additional findings from microarrays currently possible only with CVS or amniocentesis.[10,12,18,26]

The question as framed for the debate is overly ambiguous and broad. One thing that crystalized during the actual debate and subsequent audience discussion seemed to be the understanding and acceptance by the audience that, as a very generic conclusion, basic new concepts and the groundwork needed before clinical application would mostly continue to come from academia. However, once there was potential for commercialization, industry would be the more efficient driver and source of funding to bring the new technique over the finish line into routine care. As such, the audience vote was essentially a tie. It was only the perceived framing of the question that determined which part of innovation and development seemed more important to the audience members.

REFERENCES

1. Cohen, A.B. & Hanft, R.S. Technology in American Health Care:Policy Directions for Effective Evaluation and Management. . *Ann Arbor: University of Michigan Press* (2004).
2. Evans, M.I. & Hanft, R.S. The introduction of new technologies. *ACOG Clinical Review* 1997; **2**:1-14.
3. Health Technology Assessment International. http://www.htai.org.
4. Rockey, S. What are the chances of getting funded? *National Institutes of Health. Office of extramural research* http://nexus.od.nih.gov/all/2015/06/09/what-are-the-chances-of-getting-funded(2015).
5. NIH Research Portfolio Online Reporting Tools.https://report.nih.gov/success_rates/Success_ByIC.cfm [accessed on 19 August 2016].
6. Ward, B., Gersen, S.L., Carelli, M.P.,*et al.* Rapid Prenatal Diagnosis of Chromosomal Aneuploidies by Fluorescence in Situ Hybridization: Clinical Experience With 4500 Specimens. *Obstetrical & Gynecological Survey 1994;*49:163-165.
7. Lo, Y.M.D.Noninvasive prenatal detection of fetal chromosomal aneuploidies by maternal plasma nucleic acid analysis: a review of the current state of the art. *BJOG: An International Journal of Obstetrics & Gynaecology* 2008;**116**: 152-157.
8. Lo, Y.M.D, Corbetta, N., Chamberlain, P.F., *al.* Presence of fetal DNA in maternal plasma and serum. *The Lancet* 1997;**350**:485-487.
9. Bianchi, D.W., Simpson, J.L., Jackson, L.G., *et al.* Fetal gender and aneuploidy detection using fetal cells in maternal blood: analysis of NIFTY I data. *Prenatal Diagnosis 2002;* **22**:609-615.
10. Evans, M.I., Andriole, S. & Evans, S.M. Screening and Testing in Multiples. *Clinics in Laboratory Medicine* 2016;**36**:289-303.
11. Shaffer, L.G.*,* Dabell, M.P., Fisher, A.J., *et al.* Experience with microarray-based comparative genomic hybridization for prenatal diagnosis in over 5000 pregnancies. *Prenat Diagn*2012;**32**:976-985.
12. Wapner, R.J.*,* Martin, C.L., Levy, B., *et al.* Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis. *New England Journal of Medicine* 2012;**367**:2175-2184.
13. Vaiarelli, A.*,* Cimadomo, D., Capalbo, A., *et al.* Pre-implantation genetic testing in ART: who will benefit and what is the evidence? *Journal of Assisted Reproduction and Genetics* 2016;**33**:1273-1278.
14. Pinkel, D.*,* Segraves, R., Sudar, D.*, et al.* High resolution analysis of DNA copy number variation using comparative genomic hybridization to microarrays. *Nat Genet* 1998;**20**:207-11.
15. Carter, N.P., Fiegler, H. & Piper, J. Comparative analysis of comparative genomic hybridization microarray technologies: Report of a workshop sponsored by the Wellcome Trust. *Cytometry* 2002;**49**:43-48.
16. Menten, B. Emerging patterns of cryptic chromosomal imbalance in patients with idiopathic mental retardation and multiple congenital anomalies: a new series of 140 patients and review of published reports. *Journal of Medical Genetics* 2006;**43**:25-633.
17. Vissers, L.E.L.M, de Vries, B.B., Osoegawa, K., *et al.* Array-Based Comparative Genomic Hybridization for the Genomewide Detection of Submicroscopic Chromosomal Abnormalities. *The American Journal of Human Genetics* 2003;**73**:261-1270.
18. Vanakker, O.*,* Vilain, C., Janssens, S.,*et al.* Implementation of genomic arrays in prenatal diagnosis: The Belgian approach to meet the challenges. *European Journal of Medical Genetics* 2014;**57**:51-156.
19. Pollack, A. Biotech company fires chief and others over handling of data. *NY Times* **Sept 28**(2009).

20. Vandenberghe, P., Wlodarska, I., Tousseyn, T., *et al.* Non-invasive detection of genomic imbalances in Hodgkin/Reed-Sternberg cells in early and advanced stage Hodgkin's lymphoma by sequencing of circulating cell-free DNA: a technical proof-of-principle study. *Lancet Haematol* **2015;2**:e55-65.
21. Amant, F., Verheecke, M., Wlodarska, I., *et al.* Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing. *JAMA Oncology* **1**, 814 (2015).
22. Bianchi, D.W. *et al.* Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies. *JAMA* 2015;**314**:162-9.
23. Brison, N., Van Den Bogaert, K., Dehaspe, L., *et al.* Accuracy and clinical value of maternal incidental findings during noninvasive prenatal testing for fetal aneuploidies. *Genet Med* 2016
24. Gil, M.M., Quezada, M.S., Revello, R., Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2015;**45**:249-66.
25. Taylor-Phillips, S., Freeman, K., Geppert, J., *et al.* Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. *BMJ Open* 2016;**6**:e010002.
26. Evans, M.I., Wapner, R.J. & Berkowitz, R.L. Noninvasive prenatal screening or advanced diagnostic testing: caveat emptor. *American Journal of Obstetrics and Gynecology* 2016;**215**:298-305.
27. Steele, M. & Roy Breg, W. Chromosomal analysis of human amniotic-fluid cells. L*ancet* 1966;**287**:383-385.
28. Jacobson, C.B. & Barter, R.H. Intrauterine diagnosis and management of genetic defects. *Am J Obstet Gynecol*1967;**99**:96-807.
29. Philip, J., Bryndorf, T. & Christensen, B. Prenatal aneuploidy detection in interphase cells by fluorescencein situ hybridization (Fish). *Prenat Diagn* 1994;**14**:1203-1215.
30. Pertl, B., Yau, S.C., Sherlock, J., *et al.* Rapid molecular method for prenatal detection of Down's syndrome. *Lancet* 1994;**343**:1197-8.
31. Lo, Y.M., Hjelm, N.M., Fidler, C., *et al.* Prenatal diagnosis of fetal RhD status by molecular analysis of maternal plasma. *N Engl J Med* 1998;**339**:1734-8.
32. Chiu, R.W., Lau, T.K., Leung, T.N., *et al.* Prenatal exclusion of beta thalassaemia major by examination of maternal plasma. *Lancet* 2002;**360**:998-1000.
33. Schouten, J.P. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *Nucleic Acids Research* 2002;**30**:57e-57 .
34. Rickman, L. Prenatal detection of unbalanced chromosomal rearrangements by array CGH. *J Med Gen* 2005;**43**:353-361.
35. Chiu, R.W.K., Chan, K.C., Gao, Y., *et al.* Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proceed Nat Acad Sci* 2008;**105**:20458-20463.
36. Fan, H.C., Blumenfeld, Y.J., Chitkara, U., Hudgins, L. & Quake, S.R. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proceed Nat Acad Sci* 2008;**105**:16266-16271.
37. Lo, Y.M.D., Chan, K.C., Sun, H., *et al.* Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus. *Science Translational Med* 2010;**2**:61ra91-61ra91.
38. Talkowski, M.E., Ordulu, Z., Pillalamarri, V.,*et al.* Clinical Diagnosis by Whole-Genome Sequencing of a Prenatal Sample. *N Engl J Med* 2012;**367**:2226-2232.

TABLES

Table 1

NICHD GRANT FUNDING 1997 – 2015

Year	Grant proposals	Awarded	Total costs	Average award	Success Rate
1997	1438	353	$ 99,309,333.00	$281,329.56	24.6%
2000	1541	449	$ 136,172,848.00	$303,280.29	29.1%
2003	1913	508	$ 148,957,079.00	$293,222.60	26.6%
2006	2789	423	$ 141,259,518.00	$333,946.85	15.2%
2009	2784	416	$ 140,940,875.00	$338,800.18	14.9%
2012	3554	443	$ 170,466,344.00	$384,799.87	12.5%
2015	3439	397	$ 149,468,763.00	$376,495.62	11.5%

https://report.nih.gov/success_rates/Success_ByIC_Details.cfm accessed 9 21 16

Table 2

NIH GRANT FUNDING BY INSTITUTE 2015

Institute*	Grant proposals	Awarded	Total costs	Average award	Success Rate
NIAID	5932	1272	$ 577,320,121.00	$453,868.02	21.4%
NCI	9513	1236	$ 508,125,718.00	$411,104.95	13.0%
NHLBI	4233	928	$ 497,923,174.00	$536,555.14	21.9%
NIGMS	3626	1074	$ 404,894,040.00	$376,996.31	29.6%
NINDS	3992	819	$ 310,868,609.00	$379,570.95	20.5%
NICHD	3439	397	$ 149,468,763.00	$376,495.62	11.5%
NHGRI	320	60	$ 46,248,195.00	$770,803.25	18.8%

https://report.nih.gov/success_rates/Success_ByIC_Details.cfm accessed 9 21 16

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NIAID: National Institute of Allergy and Infectious Disease
NCI: National Cancer Institute
NHLBI: National Institute of Heart, Lung, and Blood Institute
NIGMS: National Institute of General Medical Sciences
NINDS: National Institute of Neurological Disorders and Stroke
NICHD: National Institute of Child Health and Human Development
NHGRI: National Human Genome Research Institute

Table 3

PRENATAL GENETIC TESTING INNOVATIONS PIONEERED IN ACADEMIA

Year	Innovation
1966	Karyotype following amniotic fluid sampling [27]
1967	First prenatal karyotype of chromosomal abnormality[28]
1970-1975	Improvements in karyotyping result in higher resolution.
1994	Fluorescent in situ hybridization (FISH) [2922]
1994	Quantitative-fluorescent PCR (qfPCR) enable aneuploidy detection in interphase nuclei [30]
1997	Discovery of cell free fetal DNA in maternal plasma[8]
1998	Non-invasive rhesus testing [31]
2002	Non-invasive detection of a monogenic disease [32]
2002	Multiplex ligation-dependent probe amplification (MLPA)[33]
2005	Array-comparative genomic hybridization (aCGH) for detection of fetal DNA copy number imbalances [34]
2008	Non-invasive fetal aneuploidy screening [35,36]
2010	Fetal genome reconstitution from cfDNA analysis using parental genotype information [37]
2015	Prenatal exome sequencing [38]